



PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 28261	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/IL2004/000890	International filing date (day/month/year) 23.09.2004	Priority date (day/month/year) 25.09.2003
International Patent Classification (IPC) or national classification and IPC A61K31/35, A61P25/16, A61P25/28, C07D327/04		
Applicant TEL AVIV UNIVERSITY FUTURE TECHNOLOGY...		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p style="margin-left: 20px;">a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 8 sheets, as follows:</p> <p style="margin-left: 40px;"><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 25.07.2005	Date of completion of this report 17.03.2006	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Baurand, P Telephone No. +49 89 2399-2156 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IL2004/000890

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-39 as originally filed

Sequence listings part of the description, Pages

1 as originally filed

Claims, Numbers

1-23 filed with telefax on 25.07.2005

Drawings, Sheets

1/15-15/15 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IL2004/000890

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9-14

because:

☒ the said international application, or the said claims Nos. 9-14 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IL2004/000890

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-4,9-14,19-23
	No: Claims	5-8,15-18
Inventive step (IS)	Yes: Claims	1-4,9-14,19-23
	No: Claims	5-8,15-18
Industrial applicability (IA)	Yes: Claims	1-8,15-23
	No: Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3.1 Claims 9 - 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 5 - 8 and 15 - 18 is not new in the sense of Article 33(2) PCT.

Claims 5 - 8 relate to an article of manufacture comprising a packaging material and compounds of formula (I). However, a claim for a package or a kit consisting of or comprising a product together with instructions for its use in a medical treatment amounts to a claim for a *first medical use*. Such a claim is not novel if it is not the first time that the product has been used in a medical treatment or pharmaceutical application.

It is pointed out that the pharmaceutical use of compounds falling under formula (I) (phenol red, pyrocatechol violet, phenolphthalein or bromophenol red) is well known and documented in the related art: phenol red serves as diagnostic aid for renal function determination, pyrocatechol violet is used for spectrophotometric determination of elements and phenolphthalein and bromophenol red are known acid/base indicators.

Because the prior art contains statements of the pharmaceutical use of the claimed compounds, novelty of claims 5 - 8 can not be acknowledged. The same reasoning applies to novelty of claims 15 - 18 relating to first medical use of compounds of formula (I).

5.2 Consequently, claims 5 - 8 and 15 - 18 also lack inventive step in the sense of Article 33(3) PCT.

5.3 For the assessment of the present claims 9 - 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not

recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observation on the international application

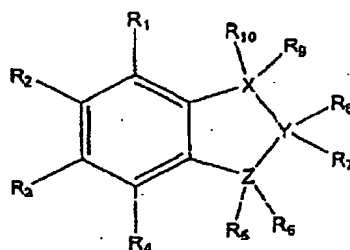
8.1 As set out in Article 6 PCT, claims shall be clear. Therefore, the meaning of the terms of a claim should be clear for the person skilled in the art from the wording of the claim alone. It is submitted that this requirement is not met in the case of claims with regard to the expressions "amyloid-destabilizing antibody", "amyloid-destabilizing peptide" and "anti-amyloid small molecule".

An attempt is made to define the compounds by their pharmacological profile, rendering the protection of said claims obscure. It is pointed out that a compound cannot be sufficiently characterised by its pharmacological profile or its mode of action. The use of such functional definitions is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature (i.e. the compounds) to which it refers.

8.2 The term "prodrug" (claims 1, 5, 9, 15 and 21) is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6.PCT).

WHAT IS CLAIMED IS:

1. Use of a compound having the general Formula I:



Formula I

a pharmaceutically acceptable salt thereof or a prodrug thereof,
wherein:

X, Y and Z are each independently selected from the group consisting of carbon, oxygen, sulfur, $CR_{11}R_{12}$ or $R_{13}R_{14}C-CR_{15}R_{16}$, provided that at least one of X, Y and Z is oxygen or sulfur; and

R_1-R_{16} are each independently selected from the group consisting of hydrogen, lone pair electrons, hydroxy, alkyl, cycloalkyl, phenyl, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol, dihydroxyphenol, aryl, alkenyl, alkynyl, heteroaryl, heteroalicyclic, halo, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, C-carboxy, O-carboxy, thiocarboxy, carbonyl, oxo, thiocarbonyl, sulfinyl, and sulfonyl, or absent, or, alternatively, at least two of R_1-R_4 and/or at least two of R_5-R_{16} form at least one five- or six-membered aromatic, heteroaromatic, alicyclic or heteroalicyclic ring,

whereas:

at least one of R_1-R_4 is selected from the group consisting of hydroxy, thiohydroxy, alkoxy, thioalkoxy, aryloxy, thioaryloxy, carboxy and thiocarboxy; and/or

at least one of R_5 - R_{16} comprises phenol, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, hydroxyphenol, and dihydroxyphenol,

with the proviso that when X is carbon and Y is $R_{13}R_{14}C-CR_{15}R_{16}$, Z is carbon or sulfur,

for the manufacture of a medicament identified for the treatment of amyloid-associated diseases.

2. The use of claim 1, wherein:

X is carbon;

Y is oxygen;

Z is carbon or sulfur; and

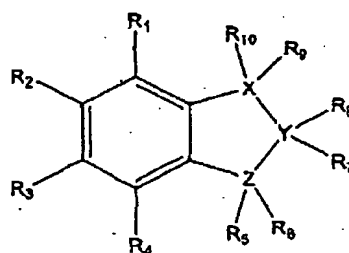
at least one of R_5 and R_6 is oxo.

3. The use of claim 2, wherein at least one of R_9 and R_{10} is selected from the group consisting of alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol and dihydroxyphenol.

4. The use of claim 1, wherein said compound is selected from the group consisting of phenol red, dimethoxy phenol red, methoxy phenol red, diacetoxy phenol red, acetoxy phenol red, pyrocatechol violet, phenolphthaleine, hydroxyphenyl, and bromophenol red.

5. An article-of-manufacture comprising a packaging material and a pharmaceutical composition identified for treating amyloid-associated diseases being contained within said packaging material, said pharmaceutical composition including, as an active ingredient, a compound having the general Formula I:

42



Formula I

a pharmaceutically acceptable salt thereof or a prodrug thereof,
wherein:

X, Y and Z are each independently selected from the group consisting of carbon, oxygen, sulfur, $\text{CR}_{11}\text{R}_{12}$ or $\text{R}_{13}\text{R}_{14}\text{C}-\text{CR}_{15}\text{R}_{16}$, provided that at least one of X, Y and Z is oxygen or sulfur; and

R_1-R_{16} are each independently selected from the group consisting of hydrogen, lone pair electrons, hydroxy, alkyl, cycloalkyl, phenyl, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol, dihydroxyphenol, aryl, alkenyl, alkynyl, heteroaryl, heteroalicyclic, halo, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, C-carboxy, O-carboxy, thiocarboxy, carbonyl, oxo, thiocarbonyl, sulfinyl, and sulfonyl, or absent, or, alternatively, at least two of R_1-R_4 and/or at least two of R_5-R_{16} form at least one five- or six-membered aromatic, heteroaromatic, alicyclic or heteroalicyclic ring,

whereas:

at least one of R_1-R_4 is selected from the group consisting of hydroxy, thiohydroxy, alkoxy, thioalkoxy, aryloxy, thioaryloxy, carboxy and thiocarboxy; and/or

at least one of R_5-R_{16} comprises phenol, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, hydroxyphenol, and dihydroxyphenol,

with the proviso that when X is carbon and Y is $\text{R}_{13}\text{R}_{14}\text{C}-\text{CR}_{15}\text{R}_{16}$, Z is carbon or sulfur, and a pharmaceutically acceptable carrier.

6. The article-of-manufacture of claim 5, wherein:

X is carbon;

Y is oxygen;

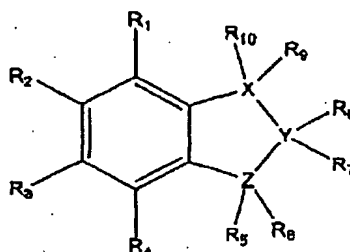
Z is carbon or sulfur; and

at least one of R_5 and R_6 is oxo.

7. The article-of-manufacture of claim 6, wherein at least one of R_9 and R_{10} is selected from the group consisting of alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol and dihydroxyphenol.

8. The article-of-manufacture of claim 5, wherein said compound is selected from the group consisting of phenol red, dimethoxy phenol red, methoxy phenol red, diacetoxy phenol red, acetoxy phenol red, pyrocatechol violet, phenolphthaleine, hydroxyphenyl, tocopherol, and bromophenol red.

9. A method of treating an amyloid-associated disease in a subject, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound having the general Formula I:



Formula I

a pharmaceutically acceptable salt thereof or a prodrug thereof,
wherein,

X, Y and Z are each independently selected from the group consisting of carbon, oxygen, sulfur, $CR_{11}R_{12}$ or $R_{13}R_{14}C-CR_{15}R_{16}$, provided that at least one of X, Y and Z is oxygen or sulfur; and

R_1-R_{16} are each independently selected from the group consisting of hydrogen, lone pair electrons, hydroxy, alkyl, cycloalkyl, phenyl, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol, dihydroxyphenol, aryl, alkenyl, alkynyl, heteroaryl, heteroalicyclic, halo, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, C-carboxy, O-carboxy, thiocarboxy, carbonyl, oxo, thiocarbonyl, sulfinyl, and sulfonyl, or absent, or, alternatively, at least two of R_1-R_4 and/or at least two of R_5-R_{16} form at least one five- or six-membered aromatic, heteroaromatic, alicyclic or heteroalicyclic ring,

whereas,

at least one of R_1-R_4 is selected from the group consisting of hydroxy, thiohydroxy, alkoxy, thioalkoxy, aryloxy, thioaryloxy, carboxy and thiocarboxy; and/or

at least one of R_5-R_{16} comprises phenol, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, hydroxyphenol, and dihydroxyphenol,

with the proviso that when X is carbon and Y is $R_{13}R_{14}C-CR_{15}R_{16}$, Z is carbon or sulfur, thereby treating the amyloid-associated disease in the subject.

10. The method of claim 9, wherein said administering is effected at a concentration of said compound not exceeding 4mg/Kg body weight/hour.

11. The method of claim 9, wherein said administering is effected orally.

12. The method of claim 9, wherein:

X is carbon;

Y is oxygen;

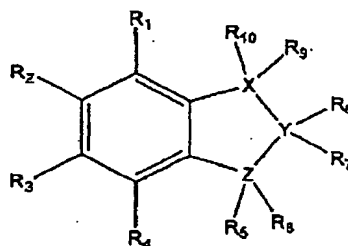
Z is carbon or sulfur; and

at least one of R_5 and R_6 is oxo.

13. The method of claim 12, wherein at least one of R_9 and R_{10} is selected from the group consisting of alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol and dihydroxyphenol.

14. The method of claim 9, wherein said compound is selected from the group consisting of phenol red, dimethoxy phenol red, methoxy phenol red, diacetoxy phenol red, acetoxy phenol red, pyrocatechol violet, phenolphthaleine, hydroxyphenyl, tocopherol, and bromophenol red.

15. A pharmaceutical composition, for use in the treatment of amyloid-associated diseases, comprising a therapeutically effective amount of a compound having the general Formula I:



Formula I

a pharmaceutically acceptable salt thereof or a prodrug thereof,
wherein,

X, Y and Z are each independently selected from the group consisting of carbon, oxygen, sulfur, $CR_{11}R_{12}$ or $R_{13}R_{14}C-CR_{15}R_{16}$, provided that at least one of X, Y and Z is oxygen or sulfur; and

R_1 - R_{16} are each independently selected from the group consisting of hydrogen, lone pair electrons, hydroxy, alkyl, cycloalkyl, phenyl, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol, dihydroxyphenol, aryl, alkenyl, alkynyl, heteroaryl, heteroalicyclic, halo, alkoxy, aryloxy, thiohydroxy, thioalkoxy,

thioaryloxy, C-carboxy, O-carboxy, thiocarboxy, carbonyl, oxo, thiocarbonyl, sulfinyl, and sulfonyl, or absent, or, alternatively, at least two of R_1 - R_4 and/or at least two of R_5 - R_{16} form at least one five- or six-membered aromatic, heteroaromatic, alicyclic or heteroalicyclic ring,

whereas:

at least one of R_1 - R_4 is selected from the group consisting of hydroxy, thiohydroxy, alkoxy, thioalkoxy, aryloxy, thioaryloxy, carboxy and thiocarboxy; and/or

at least one of R_5 - R_{16} comprises phenol, alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, hydroxyphenol, and dihydroxyphenol,

with the proviso that when X is carbon and Y is $R_{13}R_{14}C-CR_{15}R_{16}$, Z is carbon or sulfur, and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, wherein:

X is carbon;

Y is oxygen;

Z is carbon or sulfur; and

at least one of R_5 and R_6 is oxo.

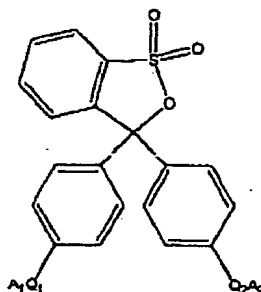
17. The pharmaceutical composition of claim 16, wherein at least one of R_9 and R_{10} is selected from the group consisting of alkoxyphenyl, thioalkoxyphenyl, aryloxyphenyl, thioaryloxyphenyl, carboxyphenyl, thiocarboxyphenyl, phenol, hydroxyphenol and dihydroxyphenol.

18. The pharmaceutical composition of claim 15, wherein said compound is selected from the group consisting of phenol red, dimethoxy phenol red, methoxy phenol red, diacetoxymphenol red, acetoxymphenol red, pyrocatechol violet, phenolphthaleine, hydroxyphenyl, tocopherol, and bromophenol red.

19. The pharmaceutical composition of claim 15, further comprising an anti-amyloid drug.

20. The pharmaceutical composition of claim 19, wherein said anti-amyloid drug is selected from the group consisting of an amyloid-destabilizing antibody, an amyloid-destabilizing peptide and an anti-amyloid small molecule.

21. A compound having the general formula II:



Formula II

a pharmaceutically acceptable salt thereof or a prodrug thereof,
wherein:

Q_1 and Q_2 are each independently selected from the group consisting of oxygen and sulfur; and

A_1 and A_2 are each independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl and carbonyl,

whereas when Q_1 and Q_2 are each oxygen, one of A_1 and A_2 is hydrogen and the other is selected from the group consisting of alkyl, cycloalkyl, aryl and carbonyl.

22. The compound of claim 21, wherein Q_1 and Q_2 are each oxygen, one of A_1 and A_2 is hydrogen and the other is methyl.

23. The compound of claim 21, wherein Q_1 and Q_2 are each oxygen, one of A_1 and A_2 is hydrogen and the other is acetyl.